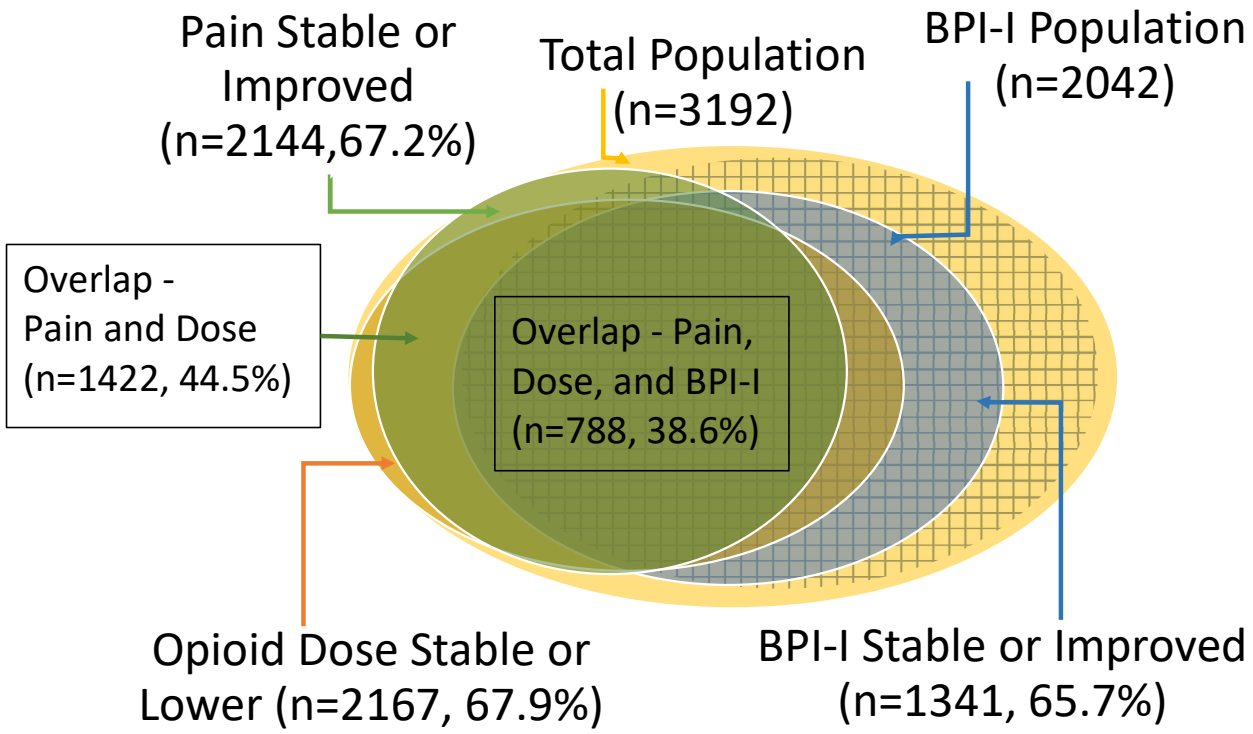
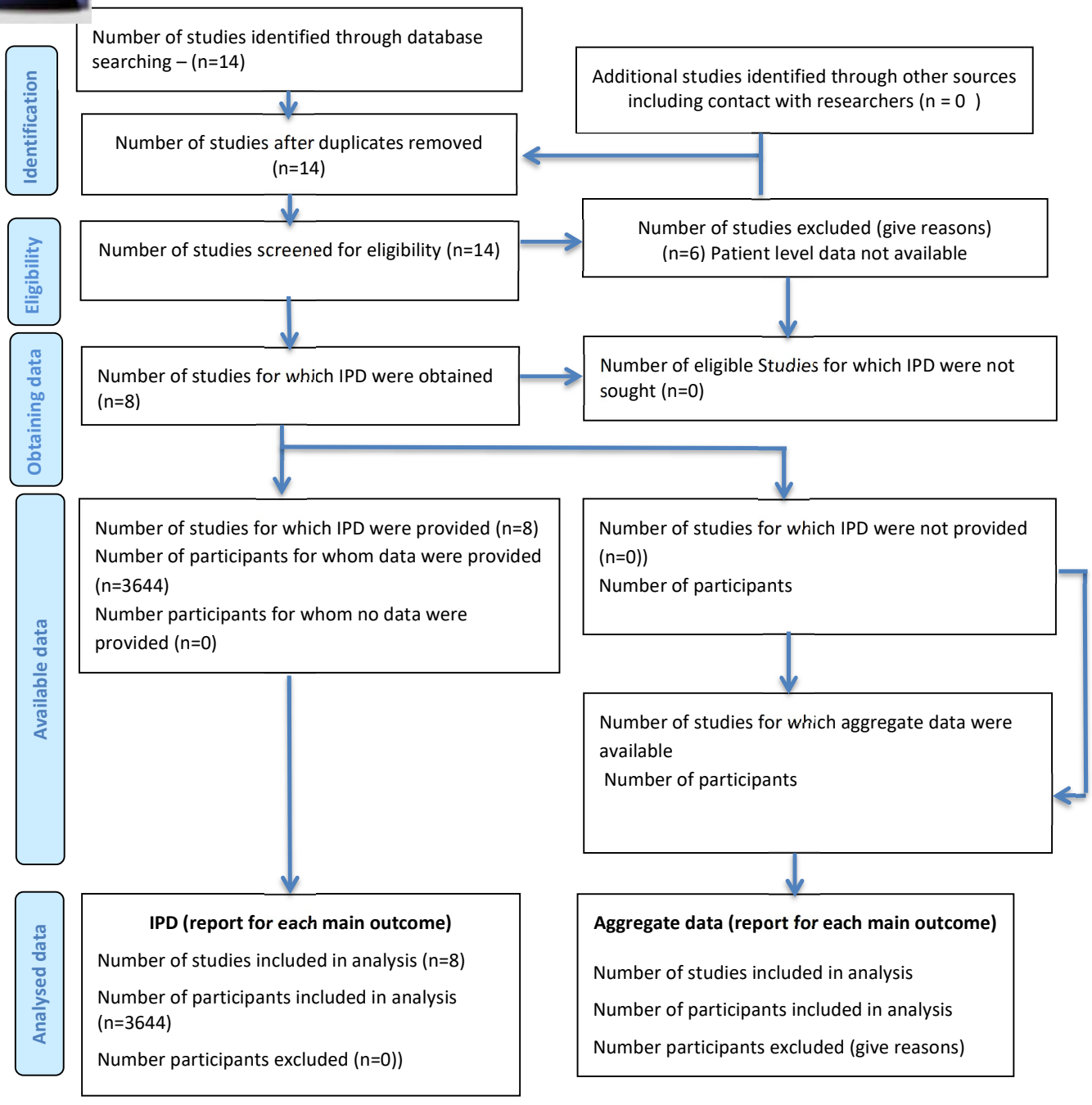
Supplemental Figure 1: Venn Diagram of Overlapping Study Groups



This chart presents a visual representation of the overlapping group analyses for Pain, Dose, and Brief Pain Inventory – Interference (BPI-I) scale (n=2040). If BPI-I is replaced by the SF-36 physical function scale (n=985), the overlapping area was 34.5%.

Supplemental Figure 2: PRISMA IPD Flow Diagram



The PRISMA IPD flow diagram

Supplemental Table 1 : Inclusion/ Exclusion Table

Category	Number of Studies	Specifics	Comments
Co-morbidities – BMI	2	Two studies specified patients must be < 45kg/m2	Remaining studies had no specific weight criteria
Co-morbidities - clinically significant diseases	8	Exclude for any significant cardiac, lung, renal, GI, liver, rhematologic diseases, or cancer.	Some studies specified additional diseases (HIV, rheumatologic, or uncontrolled endocrinologic) and some rolled the decision up into Investigator judgement about risk
Co-morbidities – Risk from hypnotics and other drugs	4	Categorical exclusion for use of MAO inhibitors (2 studies), or Phenothyazines (2 studies). High dose Hypnotics (3 studies) excluded only if investigator thought it put patient at risk.	Most studies depended on investigator judgement about specified drugs that might lead to significant risk. Few specific drugs were excluded
Drug or alcohol abuse	8	Exclude for opioid or ETOH abuse: Three specified in the last 5 years, three excluded any history, and one specified "active". Determined by UDS, or questionnaire (e.g. SOAP, COMM, ABC, Etc)	The one specifying active abuse only allowed investigator judgement to exclude patients for any perceived risk
Exception to exclusion made by Sponsor	1	Only 1 study specifically allowed application to the sponsor for exceptions for clinical issues felt to be not clinically relevant	
Hypersensitivity to study drug	7	Exclude for any evidence of hypersensitivity or intolerance of study drug(6) or any opioid (1)	
Likely to benefit from opioids	6	Six studies specifically required that investigators enroll patients had the potential to benefit from opioids	All studies specified "Investigator Opinion" in selection of patients, which would likely include the potential for benefit.
Litigation	3	Specifically excluded patients involved in litigation	
Not pregnant	8	All studies required female patients to be post-menopausal or concistent use of contraception	
Other experimental drug studies	8	Not allowed to have participated in other long acting opioid clinical trial.	
Investigators assessment of the patients risk and benefit	7	All studies had criteria measuring the patients willingness to participate, remain compliant, and report appropriately.	All studies used investigator judgement about the patients willingness, ability, and risk in participation as the primary criteria for the inclusion and required monitoring of the patient.
Pre-study opioid use	8	Oxycodone range from 10mg/d to 160mg/d in non-naïve patients	Range of opioids was considered in the analysis with results presented stratified by dose.
Pre-study non-opioid analgesic use	9	Any non-opioid analgesic was allowed pre-study and could be maintained at a stable dose through out the 12 month study.	Pre-study concomitant medications are indicated in the demographics table.

Psych-Depression	8	All studies state psychiatric disease or suicidality was a reason for excludion but left up to the investigator to assess. One study specified a HADs score >12 in addition to poorly controlled symptoms.	Number of patients enrolled with a history of depression are listed in the demographics table. All studies allowed stable controlled depression patients to be enrolled and remain on their medications through the study.
Roll-over Issue	3	For the three studies that allowed rollover patients from the previous 12 week randomized trial, they required that the patients successfully complete the 12 week trial	
Sex-Age	8	All studies required patients to be >18 years old with an upper limit of 75-80 years or not specified	Investigator judgement was the primary criteria for the inclusion of older people.
Stable - Other drugs – Treatment	5	Five studies specifically allowed concomitant medications to be taken in a stable manner	Decision about additional concomitant medications was left up to the investigator in the other three trials
Surgery recent	6	Six specifically excuded (or delayed) enrollment for people having surgery within 2-3 months.	Investigator judgement was the primary criteria for the inclusion of patients including any reason the patient may not be appropriate, including surgical history. One study specifically excluded patients with more than 2 back surgeries
Type of Pain - Specific	7	All studies excluded patients with joint or back pain thought to be due to systemic disease, including rheumatologic disease. Patients with primarily neuropathic pain were excluded but allowed if it was not the predominate pain	Number of people with neuropathic component to their pain is reported in the demographics table
UDS	4	All except the Oxycodone/ Naloxone studies required a baseline UDS.	All studies used investigator judgement as the primary criteria for the inclusion and monitoring of patients .
Investigators assessment of the patients	7	All studies had criteria measuring the patients willingness to participate, remain compliant, and report appropriately. Four studies asked specifically about patients willingness to discontinue their opioid during the titraion portion.	All studies used investigator judgement about the patients willingness, ability, and risk in participation as the primary criteria for the inclusion and monitoring of patients.

Supplemental Table 2 – Study Characteristics

Brand (Study Date)	Compound	Opioid Use Defining Non-Naive	Minimum Opioid Dose/Day	Concomitant Meds Days Stable	Rescue Medication*	Doses of Drug in mg.
Hysingla (2011-13)	Hydrocodone	Any use last 14 days	>0 mgs	30	Given by investigator without being recorded.	20,40,60,80,120 given once a day Max 120/day
Vantrela (2010-12)	Hydrocodone	Any use last 14 Days	>10 mgs	14	Hydrocodone -APAP 5/325 mg. Average 3 pills/ wk.	15, 30, 45, 60, 90 given twice a day Max 180/day
Zohydro (2010-11)	Hydrocodone	Any use last 28 Days	>45 mgs	14	Hydrocodone -APAP 5/325 mg Average 1.5 pills/ day	10, 20, 30, 40, 50 given twice a day Max 100/day
Targiniq (2006-08)	Oxycodone (Naloxone)	Any use last 1 month	>20 mgs	14-30	Prestudy rescue use reported at baseline and allowed during study	10/5, 20/10, 40/20 given twice a day Max 80/day
Targiniq (2006-08)	Oxycodone (Naloxone)	Any use last 1 month	>20 mgs	14-30	Prestudy rescue use reported at baseline and allowed during study	10/5, 20/10, 40/20 given twice a day Max 80/day
Targiniq (2005-07)	Oxycodone (Naloxone)	Any use last 1 month	>20 mgs	14-30	Only acetaminophen	10/5, 20/10, 40/20 given twice a day Max 80/40day
Troxyca (2010-12)	Oxycodone (Naltrexone)	Any use	>0 mgs	14	Only acetaminophen	10/1.2, 20/2.4, 30/3.6, 40/4.8, 60/7.2, 80/9.6 given twice a day Max 160/19.2
Remoxy (2006-08)	Oxycodone	Any use	>0 mgs	28	Acetaminophen/ NSAIDs without being recorded	10, 15, 20, 30, 40 given twice a day Max 80/day

Hydrocodone | Oxycodone group | Oxycodone Constipation group | Oxycodone Pain group

*Note: in all studies patients were encouraged to seek increase in extended release study drug rather than take rescue medication for pain control

Supplemental Table 3: Maintenance Period Dropouts

Study Phase	**Titration**	**Maintenance Dropouts by Study Type**					**Both Phases**
Drug	**Dropouts**	**Hydrocodone**	**Oxycodone**	**All**	**Oxycodone**	**Sub-Total**	**Dropouts**
Indication	All Studies	Pain	Pain	Pain	Constipation	All Studies	All Studies
Number	(n=3957)	(n=1427)	(n=1311)	(n=2738)	(n=454)	(n=3192)	(n=3957)
Disposition Categories							
Completed Study	3192 (80.7%)	860 (60.3%)	832 (63.5%)	1692 (61.8%)	399 (87.9%)	2091 (65.5%)	2091 (52.8%)
Dropouts	765 (19.3%)	567 (39.7%)	479 (36.5%)	1046 (38.2%)	55 (12.1%)	1101 (34.5%)	1866 (47.2%)
Titration Failures	14 (0.4%)						
Lack of Efficacy	66 (1.7%)	27 (1.9%)	54 (4.1%)	81 (3.0%)	4 (0.9%)	85 (2.7%)	151 (3.8%)
Patient Withdrawal	121 (3.1%)	125 (8.8%)	113 (8.6%)	238 (8.7%)	15 (3.3%)	253 (7.9%)	374 (9.5%)
Adverse Event	328 (8.3%)	185 (13.0%)	144 (11.0%)	329 (12.0%)	16 (3.5%)	345 (10.8%)	673 (17.0%)
Non-Compliance	70 (1.8%)	60 (4.2%)	53 (4.0%)	113 (4.1%)	0 (0.0%)	113 (3.5%)	183 (4.6%)
Protocol Violation	70 (1.8%)	35 (2.5%)	9 (0.7%)	44 (1.6%)	0 (0.0%)	44 (1.4%)	114 (2.9%)
Sponsor Request	10 (0.3%)	0 (0.0%)	11 (0.8%)	11 (0.4%)	0 (0.0%)	11 (0.3%)	21 (0.5%)
Investigator Option	36 (0.9%)	51 (3.6%)	23 (1.8%)	74 (2.7%)	15 (3.3%)	89 (2.8%)	125 (3.2%)
Suspected Diversion	9 (0.2%)	15 (1.1%)	2 (0.2%)	17 (0.6%)	0 (0.0%)	17 (0.5%)	26 (0.7%)
Deaths	2 (0.1%)	9 (0.6%)	5 (0.4%)	14 (0.5%)	2 (0.4%)	16 (0.5%)	18 (0.5%)
Other	7 (0.2%)	10 (0.7%)	10 (0.8%)	20 (0.7%)	0 (0.0%)	20 (0.6%)	27 (0.7%)
Loss to Followup	32 (0.8%)	50 (3.5%)	55 (4.2%)	105 (3.8%)	3 (0.7%)	108 (3.4%)	140 (3.5%)